

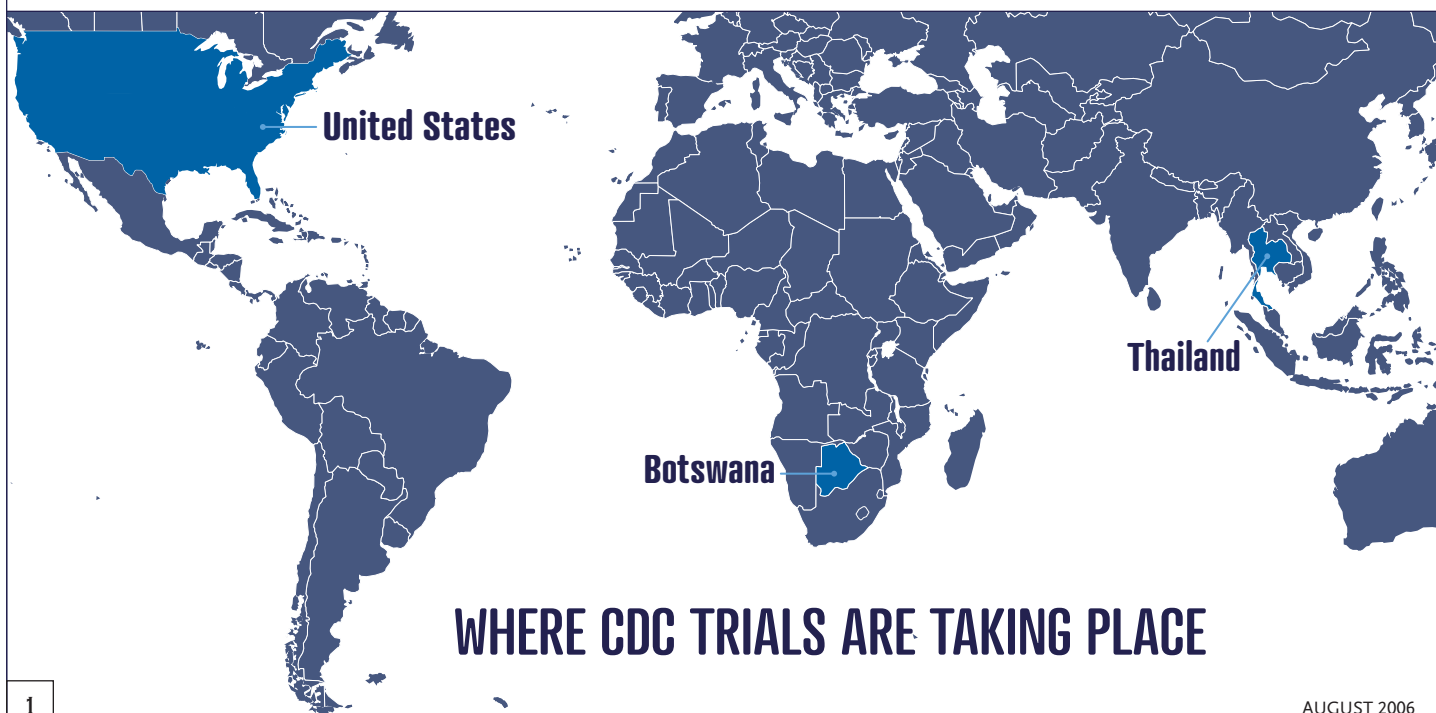
CDC TRIALS OF PRE-EXPOSURE PROPHYLAXIS FOR HIV PREVENTION

Clinical Trials in Botswana, Thailand, and the United States

New approaches to HIV prevention are urgently needed to stem the estimated four million new HIV infections that occur worldwide each year. While behavior change programs have contributed to dramatic reductions in the number of annual infections in the U.S. and many other nations, far too many individuals remain at high risk. With an effective vaccine years away, there is mounting evidence that antiretroviral drugs may be able to play an important role in reducing the risk of HIV infection. As part of its commitment to developing new HIV prevention strategies, the Centers for Disease Control and Prevention (CDC) is sponsoring three clinical trials of pre-exposure prophylaxis, or PrEP, for HIV prevention. The trials test the antiretroviral drug tenofovir disoproxil fumarate (or tenofovir, brand name Viread®) used alone or in combination with emtricitabine (together, known as the brand name Truvada®) taken as a preventative.

The trials are designed to answer important questions about the safety and efficacy of a tenofovir or tenofovir plus emtricitabine pill taken as a daily oral HIV preventative among three populations at high risk for infection: heterosexuals in Botswana, intravenous drug users in Thailand, and men who have sex with men (MSM) in the United States. The trials in Botswana and Thailand are safety and efficacy trials, while the U.S. trial is an extended safety trial. All three sites will also assess the effects of taking a daily pill on HIV risk behaviors, adherence to and acceptability of the regimen, and in cases where participants become HIV infected, the resistance characteristics of the acquired virus. This information will be critical to guide future studies and HIV prevention programs.

Similar PrEP trials are also being conducted by other agencies. Family Health International, with funding from the Bill and Melinda Gates Foundation, has completed a safety trial of tenofovir for HIV prevention among young women in Ghana. That trial will soon provide important data on the safety and acceptability of a once-daily PrEP regimen. Additionally, the National Institutes of Health will be conducting a PrEP safety and efficacy trial among MSM in Peru.





Rationale for Trials of Pre-Exposure Prophylaxis for HIV Prevention

Researchers believe that an antiretroviral drug taken as a daily oral preventative is one of the most important new prevention approaches being investigated today. An effective daily preventative could help address the urgent need for female-controlled prevention methods and, when combined with existing prevention measures, could help reduce new HIV infections among men and women at high risk.

The concept of providing a preventative treatment before exposure to an infectious agent is not new. For example, when individuals travel to an area where malaria is common, they are advised to take medication to fight malaria before and during travel to that region. The medicine to prevent illness is then already in their bloodstream if they are exposed to the infectious agent that causes malaria.

Several sources of data suggest that the use of antiretroviral drugs in this manner may be effective in reducing the risk of HIV infection. Theoretically, if HIV replication can be inhibited from the very first moment the virus enters the body, it may not be able to establish a permanent infection. Providing antiretrovirals (ARVs) to HIV-infected women during labor and delivery and to their newborns immediately following birth has been shown to reduce the risk of mother-to-child transmission by about 50%. Additionally, in observational studies, ARV regimens have been associated with an 80% reduction in the risk of HIV infection among health care workers following needle sticks and other accidental exposures, when treatment is initiated promptly and continued for several weeks. Finally, animal studies have shown that tenofovir can reduce the transmission of a virus similar to HIV in monkeys when given before and immediately after a single retroviral exposure. An animal study also demonstrated that pre-exposure injections with tenofovir plus emtricitabine protected monkeys from multiple exposures to an HIV-like virus. These data, combined with the drugs' favorable resistance and safety profiles as HIV treatments, make tenofovir and tenofovir plus emtricitabine ideal candidates for HIV prevention trials.

Characteristics of Current PrEP Candidates

- Established safety as HIV treatments
- Potent antiretrovirals
- Long duration of action
- Once-daily dosing
- Low levels of resistance

Tenofovir was approved by the U.S. Food and Drug Administration in 2001 as a treatment for HIV infection, and the tenofovir plus emtricitabine combination pill was approved for use as an HIV treatment in 2004. More than 150,000 HIV-infected people around the world have now used these drugs. As treatments for HIV-infected individuals, tenofovir and tenofovir plus emtricitabine have been shown to be both safe and effective. They have relatively low levels of side effects and slow development of associated drug resistance, compared with other available HIV treatments. Because the therapies are taken orally only once a day, with or without food, they are also among the most convenient-to-use HIV drugs available today. These trials are designed to evaluate the drugs' safety and efficacy among uninfected individuals. Side effects may differ in HIV-negative populations, and it is not yet known if tenofovir or tenofovir plus emtricitabine can prevent HIV infection in humans.



Specific Trial Designs and Objectives

All three of CDC's studies are randomized, double-blind, placebo-controlled trials. In each trial, all participants will receive risk-reduction counseling and other prevention services. In addition, half of the participants will be randomly assigned to receive one antiretroviral pill daily (either tenofovir or tenofovir plus emtricitabine, depending on the trial), and the other half will be randomly assigned to take one daily placebo pill (a similar tablet without active medication). Neither researchers nor participants will know an individual's group assignment. In all, the studies will involve 3,200 volunteers. The Thailand and U.S. trials of tenofovir began in 2005 and the Botswana trial of tenofovir plus emtricitabine is scheduled to begin in late 2006. The trials are expected to last between 2 and 4 years.

To ensure that the studies remain on a solid scientific and ethical foundation, all study procedures and plans are reviewed and approved by scientific and ethical review committees at CDC (called institutional review boards, or IRBs), as well as IRBs established by each host country and research site prior to trial launch. Additionally, data on safety, enrollment, and efficacy will be reviewed at standard intervals by an independent data safety and monitoring board (DSMB) for the Botswana and Thai trials, and by an independent safety review committee for the U.S. trial. These committees review emerging data to ensure that continuing the trial is safe and to determine the point at which the results are conclusive. If scientific questions arise during the course of the research, these committees will meet more frequently.

Botswana and Thailand

The trials in Botswana and Thailand are safety and efficacy trials. The Botswana trial is examining the safety and efficacy of tenofovir plus emtricitabine, and the Thailand trial is examining the safety and efficacy of tenofovir.



■ **Botswana** — The Botswana study is being conducted in collaboration with the Botswana government and will enroll 1,200 HIV-negative heterosexual men and women, ages 18 to 29, in the nation's two largest cities, Gaborone and Francistown. Participants will be recruited through a number of venues, including HIV voluntary counseling and testing centers, sexually transmitted disease (STD) and family planning clinics, youth organizations, and community events.

■ **Thailand** — The Thailand study is being conducted in collaboration with the Bangkok Metropolitan Administration and the Thailand Ministry of Public Health and is enrolling 1,600 HIV-negative intravenous drug users (IDUs) at 17 drug treatment



clinics in Bangkok. Participants will be recruited at the drug treatment clinics, at community outreach sites, and through a peer referral program.



The United States

The U.S. trial is designed to assess the clinical and behavioral safety of once-daily tenofovir among HIV-negative MSM. This trial will not be large enough to evaluate the drug's efficacy in reducing HIV transmission. *(Note: The efficacy of a once-daily PrEP regimen among MSM in Peru is being evaluated independently by the National Institutes of Health.)* Data from the CDC trial will assist in the design of future studies among MSM, and will provide critical information to guide the development of guidelines for use, should efficacy be demonstrated in other trials.

■ **United States** — The U.S. study is being conducted at two sites in collaboration with the San Francisco Department of Public Health and the AIDS Research Consortium of Atlanta. The study will enroll 400 HIV-negative MSM who report having had anal intercourse in the past 12 months. Participants will be randomly assigned to one of four study arms. Two arms will receive either tenofovir or placebo immediately, while the other two arms will receive either tenofovir or placebo after nine months of enrollment. This design will allow researchers to compare risk behaviors among those taking a daily pill and those not taking pills.



CDC is also in the planning stages for a separate trial to assess the safety of tenofovir plus emtricitabine in HIV-uninfected individuals. Potential sites for this study are still being evaluated.

Education and Enrollment of Trial Participants

Understanding the potential impact of a daily drug regimen on HIV risk behaviors will be critical, should pre-exposure prophylaxis prove effective in reducing HIV transmission. One of the greatest risks, as efforts progress to identify new biomedical approaches, is that individuals at risk will reduce their use of proven HIV prevention strategies. It will therefore be crucial to reinforce proven behavioral prevention strategies, both within and beyond these trials. All three trials will take multiple steps to address this issue during the education and enrollment of trial participants and through ongoing participant counseling.

First, it is critical to ensure that participants understand that trial participation may not protect them from HIV infection—either because they may receive a placebo or because they may receive a study drug, the efficacy of which remains unproven. This and other key aspects of the trial, including the potential risks and benefits of participation, are explained to potential volunteers in depth in the language of their choice, prior to their enrollment. To ensure participants fully understand all aspects of their participation, all volunteers will be required to pass a comprehension test prior to providing written informed consent. Study participants are also free to withdraw from the trial at any time and for any reason.



Risk-Reduction Counseling and Other Prevention and Treatment Services

To assist participants in eliminating or reducing HIV risk behaviors, extensive counseling is provided at each study visit, and more often if needed. The interactive counseling provided has proven effective in reducing the risk of HIV and other STDs in multiple populations, including past participants of similar HIV prevention trials. Participants are also offered free condoms and STD testing and treatment to reduce their risk for HIV infection. Additionally, in Thailand, participating IDUs are offered follow-up in a methadone drug treatment program and receive bleach and instructions on how to use it to clean needles. Consistent with Thai government policy, sterile syringes are not provided, but are widely available in Thailand without a prescription and at low cost (one sterile syringe and one needle cost about 5 baht, or about \$0.12).

While participants will likely be at lower risk as a result of these prevention services, some individuals will engage in behavior that places them at risk for HIV infection. To ensure that participants who are infected during the trial are quickly referred to the best available medical and psychosocial services, participants will receive free rapid HIV testing at every visit. This regular HIV testing will also help guard against the development of drug-resistant virus, as the study drug will be immediately discontinued when infection is detected.

Participants who become infected will receive confirmatory testing for infection, post-test risk-reduction and support counseling, and help enrolling in local HIV care programs. Both Thailand and Botswana have anti-retroviral treatment and HIV care programs in place at minimal or no cost to patients. In the United States, participants will be referred to local health care providers or public programs for needed medical and social services.

Additionally, to help guide treatment decisions and to determine if prior exposure to tenofovir or tenofovir plus emtricitabine has any effect on the course of disease, initial testing will be provided for viral load, CD4 count, and HIV resistance mutations. Participants will also be followed for an additional 12 months following infection to examine their immune and virologic response. Although study procedures will ensure a very low risk of drug-resistant virus emerging, the initial HIV resistance testing will provide important data on the degree to which any resistance does occur.

Monitoring for Side Effects

The health of participants will be closely monitored throughout the trial, and participants will be linked to any necessary medical care as needed. In addition to scheduled reviews of safety data by the DSMB, both clinical and behavioral safety will be closely monitored on an ongoing basis.

Although the drugs being tested have excellent safety profiles, there are potential medical risks. Tenofovir has been associated with minor side effects such as nausea, vomiting, and loss of appetite, as well as rare but more serious effects, such as impaired kidney function or reductions in bone density. Tenofovir plus emtricitabine has similarly been associated with a relatively low level of side effects, including diarrhea, nausea, fatigue, headache, dizziness, and rash, with infrequent reports of more serious side effects, such as impaired kidney function and lactic acidosis (a build-up of lactic acid in the blood). For both drugs, these effects have largely been reversed after use of the drug was discontinued.



Careful monitoring will be provided using laboratory testing for any biological abnormalities (such as elevated creatinine or decreased phosphorus), so that the drug being tested can be promptly discontinued if serious concerns are identified. CDC will work with partners in each community to ensure that care is provided if either drug results in any health problems during the trial.

Community Involvement

CDC has and will continue to work closely with community partners at each research site to ensure active community participation during the planning and implementation of these trials.

■ **Botswana** — In Botswana, community advisory boards have been established at each site, which include representatives from local governments (elected and traditional), as well as community members and representatives from key stakeholder organizations. These groups will provide input to researchers throughout the trial. Participant advisory boards will also be set up when the trial begins.

■ **Thailand** — In Thailand, a community relations committee, made up of intravenous drug users from each of the 17 drug treatment centers, family members, and representatives of local community organizations, meets regularly and provides advice to study staff on all aspects of study design and implementation. Additionally, a community liaison serves as a bridge between researchers and community organizations, responding to questions or concerns throughout the trial.

■ **United States** — In the United States, both sites have established active community advisory boards that are consulted regularly about study procedures and educational materials for potential participants. Members of these boards will provide ongoing advice throughout the trials.

In addition to the regular input received by these established committees, broader outreach and consultations with advocates and community-based organizations representing populations at risk for HIV are being held, as needed, to address current and future plans for HIV prevention research and programs.

Next Steps in HIV Prevention

As we move forward with our search for new HIV prevention strategies, it will be critical to determine how these approaches can best be integrated into existing programs, should they prove effective in reducing risk. Because no strategy will be 100% effective in preventing HIV infection, future impact will ultimately be determined by how effectively strategies are used in combination to provide the greatest protection to individuals at risk. CDC, in collaboration with the World Health Organization, the National Institutes of Health, other research organizations, and community stakeholders worldwide, is developing plans to quickly respond to emerging data from these and other HIV prevention trials. These collaborations will help guide the development of future policies and programs that can most effectively reduce the toll of HIV and AIDS.